

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Schiemann et al.

Group Art Unit: 1625

Serial No.: 10/583,689

Examiner: Rita J. Desai

Filed: Dec. 14, 2004

For: 2-(Hetero)-aryl substituted tetrahydroquinoline

**DECLARATION UNDER 37 C.F.R. § 1.132**

Honorable Commissioner of  
Patents and Trademarks  
Washington, D.C. 20231

SIR:

Jan Hauß, being duly warned, deposes and says:

*I am a citizen of Germany residing at Langen, Germany;*

*I am a chemist by training and experience;*

*the degree of Dr. rer. nat. was bestowed on me by the University of Heidelberg, Germany in 1993;*

*from 1993 to 1994 I was employee at the Institute for Chemistry, University of Heidelberg, Germany;*

*from 1995 to 1996 I was scientist at the Department of Chemistry, University of Sussex, UK;*

*from 1996 to 1998 I was employee at the IBM Informationssysteme Deutschland GmbH, Frankfurt Germany;*

*from May 1998 to 2007 I was Head of a NMR laboratory of Merck KGaA, Darmstadt, Germany;*

*since March 2007 I am involved in analytical IT Projects at Merck KGaA, Darmstadt, Germany;*

*I am author or co-author of numerous papers and patents in the fields of chemistry and NMR.*

The analytical results presented below for the present application prove that the claimed compounds have been prepared and possess the disclosed chemical structure.

I have carried out, or supervised experiments for analyzing the compounds according to the methods described within the genus claimed in the pending application.

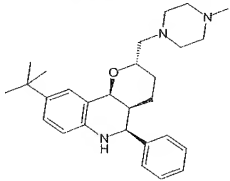
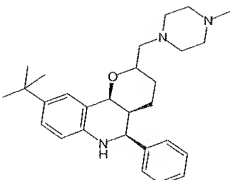
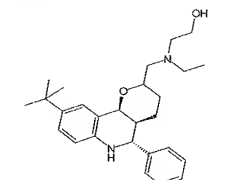
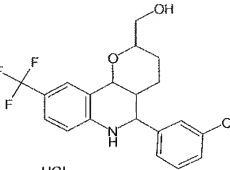
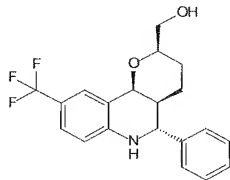
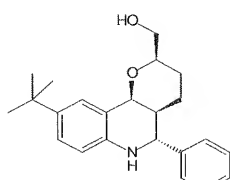
### **Report on NMR analytics**

NMR (1H) was performed by using the following equipment and parameter

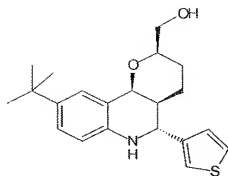
- Devices: Bruker Avance DRX 500  
(Bruker Avance 400)  
(Bruker DPX 300)
- Reference: TMS
- TD (Time Domaine = number of data points or digital resolution): 65536
- Solvent: DMSO d6
- NS (Number of Scans): 32
- SF (Spectrometer Frequence): 500 MHz
- TE (Temperature): 303 K

The NMR data of the analytical report (Table I) show the compounds tested and their NMR values. The "no." refers to present application where compounds are disclosed.

**Table I:** NMR values of compounds for Eg5 inhibition

No.	CHEMISTRY	NMR
133		$^1\text{H}$ NMR (500 MHz, DMSO) $\delta$ = 7.29 (t, $J$ =7.5, 2H), 7.25-7.15 (m, 5H), 7.07-7.02 (m, 1H), 6.60 (d, $J$ =8.4, 1H), 6.20 (d, $J$ =2.4, 1H), 4.35 (d, $J$ =5.0, 1H), 4.25 (s, 1H), 3.59-3.50 (m, 1H), 2.47-2.15 (m, 9H), 2.12 (s, 3H), 2.10-2.04 (m, 1H), 1.84-1.70 (m, 1H), 1.64-1.53 (m, 1H), 1.52-1.37 (m, 1H), 1.32-1.16 (m, 10H).
	Chemistry 76	
153		$^1\text{H}$ NMR (500 MHz, DMSO) $\delta$ = 7.29 (t, $J$ =7.5, 2H), 7.25-7.16 (m, 5H), 7.07-7.00 (m, 1H), 6.60 (d, $J$ =8.4, 1H), 6.20 (d, $J$ =2.4, 1H), 4.35 (d, $J$ =5.0, 1H), 4.25 (s, 1H), 3.57-3.51 (m, 1H), 2.47-2.16 (m, 9H), 2.12 (s, 3H), 2.10-2.02 (m, 1H), 1.81-1.72 (m, 1H), 1.64-1.54 (m, 1H), 1.49-1.38 (m, 1H), 1.32-1.18 (m, 10H).
	Chemistry 55	
159		$^1\text{H}$ NMR (500 MHz, DMSO) $\delta$ = 9.09 (d, $J$ =33.6, 1H), 7.46-7.36 (m, 4H), 7.33 (t, $J$ =7.1, 1H), 7.14 (dd, $J$ =8.7, 2.2, 1H), 7.04 (d, $J$ =8.5, 1H), 6.54 (d, $J$ =8.5, 1H), 5.94 (s, 1H), 5.26 (s, 1H), 4.44-4.41 (m, 2H), 4.07 (t, $J$ =10.5, 1H), 4.03 (q, $J$ =7.1, 2H), 3.77-3.69 (m, 3H), 3.25-3.15 (m, 2H), 1.97-1.88 (m, 1H), 1.71-1.62 (m, 1H), 1.57-1.44 (m, 1H), 1.37-1.26 (m, 2H), 1.23 (s, 9H), 1.17 (t, $J$ =7.1, 3H).
	Chemistry 49	
209	 HCl	$^1\text{H}$ NMR (500 MHz, DMSO, trans-Isomer, racemic) $\delta$ = 9.39 (s, 1H), 7.34 (s, 1H), 7.27 (dd, $J$ =8.6, 1.9, 1H), 7.18 (t, $J$ =7.7, 1H), 6.85-6.80 (m, 3H), 6.75-6.68 (m, 2H), 4.59 (t, $J$ =5.8, 1H), 4.45 (d, $J$ =11.4, 1H), 4.41 (d, $J$ =2.2, 1H), 3.68-3.56 (m, 1H), 3.47-3.41 (m, 1H), 3.41-3.34 (m, 1H), 1.84-1.75 (m, 1H), 1.70-1.57 (m, 1H), 1.54-1.42 (m, 1H), 1.35 (t, $J$ =12.9, 2H).
	Chemistry 586	
225		$^1\text{H}$ NMR (500 MHz, DMSO) $\delta$ = 7.47-7.38 (m, 4H), 7.37-7.33 (m, 2H), 7.28 (dd, $J$ =8.6, 1.9, 1H), 6.86 (s, 1H), 6.71 (d, $J$ =8.5, 1H), 4.60 (t, $J$ =5.8, 1H), 4.56 (d, $J$ =11.5, 1H), 4.43 (d, $J$ =2.2, 1H), 3.66-3.58 (m, 1H), 3.45 (dt, $J$ =11.2, 5.6, 1H), 3.38 (dt, $J$ =11.1, 5.3, 1H), 1.92-1.85 (m, 1H), 1.69-1.58 (m, 1H), 1.55-1.43 (m, 1H), 1.38-1.25 (m, 2H).
	Chemistry 104	
248		$^1\text{H}$ NMR (500 MHz, DMSO) $\delta$ = 7.45-7.35 (m, 4H), 7.35-7.28 (m, 1H), 7.08-7.02 (m, 2H), 6.57-6.51 (m, 1H), 5.89 (s, 1H), 4.59 (t, $J$ =5.8, 1H), 4.51 (d, $J$ =11.4, 1H), 4.34 (d, $J$ =2.3, 1H), 3.64-3.57 (m, 1H), 3.45 (dt, $J$ =11.1, 5.5, 1H), 3.38 (dt, $J$ =11.1, 5.5, 1H), 1.90-1.80 (m, 1H), 1.66-1.57 (m, 1H), 1.55-1.43 (m, 1H), 1.30 (t, $J$ =14.9, 2H), 1.21 (s, 9H).
	Chemistry 277	

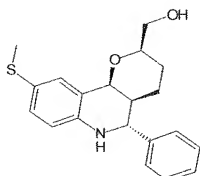
265



Chemistry 588

$^1\text{H}$  NMR (500 MHz, DMSO)  $\delta$  = 7.53 (dd,  $J$ =4.9, 3.0, 1H), 7.50-7.48 (m, 1H), 7.15 (dd,  $J$ =4.9, 1.0, 1H), 7.04-7.00 (m, 2H), 6.54-6.51 (m, 1H), 5.84 (s, 1H), 4.65 (d,  $J$ =11.4, 1H), 4.57 (t,  $J$ =5.8, 1H), 4.32 (d,  $J$ =2.6, 1H), 3.63-3.54 (m, 1H), 3.48-3.39 (m, 1H), 3.38-3.32 (m, 1H), 1.87-1.80 (m, 1H), 1.63 (tt,  $J$ =13.1, 4.4, 1H), 1.45 (td,  $J$ =13.2, 3.6, 1H), 1.40-1.27 (m, 2H), 1.22 (s, 9H).

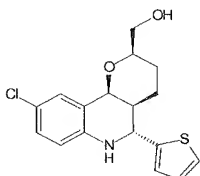
271



Chemistry 164

$^1\text{H}$  NMR (500 MHz, DMSO)  $\delta$  = 7.45-7.36 (m, 4H), 7.35-7.30 (m, 1H), 7.09 (d,  $J$ =1.9, 1H), 7.03 (dd,  $J$ =8.4, 2.1, 1H), 6.57 (d,  $J$ =8.4, 1H), 6.21 (s, 1H), 4.58 (s, 1H), 4.50 (d,  $J$ =11.4, 1H), 4.34 (d,  $J$ =1.9, 1H), 3.64-3.54 (m, 1H), 3.44 (dd,  $J$ =11.1, 5.4, 1H), 3.40-3.32 (m, 1H), 2.35 (s, 3H), 1.85 (d,  $J$ =11.3, 1H), 1.66-1.56 (m, 1H), 1.52-1.39 (m, 1H), 1.29 (t,  $J$ =16.2, 2H).

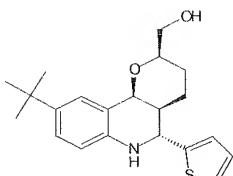
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Chemistry 142

$^1\text{H}$  NMR (500 MHz, DMSO)  $\delta$  = 7.51 (d,  $J$ =5.0, 1H), 7.16 (d,  $J$ =3.2, 1H), 7.08 (d,  $J$ =2.4, 1H), 7.05-7.00 (m, 2H), 6.62 (d,  $J$ =8.7, 1H), 6.52 (s, 1H), 4.83 (d,  $J$ =11.2, 1H), 4.58 (t,  $J$ =5.8, 1H), 4.36 (d,  $J$ =2.2, 1H), 3.63-3.54 (m, 1H), 3.47-3.40 (m, 1H), 3.37-3.32 (m, 1H), 1.77-1.73 (m, 1H), 1.72-1.60 (m, 1H), 1.50-1.39 (m, 2H), 1.38-1.29 (m, 1H).

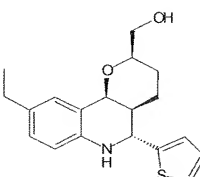
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Chemistry 254

$^1\text{H}$  NMR (500 MHz, DMSO)  $\delta$  = 7.48 (d,  $J$ =5.0, 1H), 7.13 (d,  $J$ =3.0, 1H), 7.07-6.99 (m, 3H), 6.55 (d,  $J$ =8.3, 1H), 6.13 (s, 1H), 4.84 (d,  $J$ =11.1, 1H), 4.59 (t,  $J$ =5.7, 1H), 4.33 (d,  $J$ =2.0, 1H), 3.66-3.54 (m, 1H), 3.46-3.40 (m, 1H), 3.39-3.33 (m, 1H), 1.78-1.58 (m, 2H), 1.54-1.39 (m, 2H), 1.39-1.28 (m, 1H), 1.22 (s, 9H).

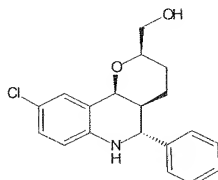
329



Chemistry 240

$^1\text{H}$  NMR (500 MHz, DMSO)  $\delta$  = 7.50 (d,  $J$ =5.0, 1H), 7.14 (d,  $J$ =3.1, 1H), 7.03 (dd,  $J$ =4.9, 3.5, 1H), 6.90 (s, 1H), 6.88-6.84 (m, 1H), 6.55 (d,  $J$ =8.2, 1H), 6.12 (s, 1H), 4.84 (d,  $J$ =11.1, 1H), 4.58 (t,  $J$ =5.8, 1H), 4.33 (d,  $J$ =2.1, 1H), 3.62-3.57 (m, 1H), 3.44 (quint,  $J$ =5.5, 1H), 3.40-3.32 (m, 1H), 2.46 (q,  $J$ =7.6, 2H), 1.74 (d,  $J$ =11.1, 1H), 1.71-1.61 (m, 1H), 1.51-1.40 (m, 2H), 1.39-1.29 (m, 1H), 1.13 (t,  $J$ =7.6, 3H).

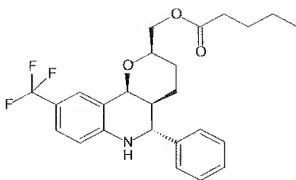
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Chemistry 192

$^1\text{H}$  NMR (500 MHz, DMSO)  $\delta$  = 7.46-7.28 (m, 5H), 7.07 (s, 1H), 7.00 (d,  $J$ =8.2, 1H), 6.60 (d,  $J$ =8.5, 1H), 6.30 (s, 1H), 4.58 (s, 1H), 4.48 (d,  $J$ =11.2, 1H), 4.35 (s, 1H), 3.63-3.55 (m, 1H), 3.52-3.40 (m, 2H), 1.85 (d,  $J$ =9.5, 1H), 1.66-1.55 (m, 1H), 1.51-1.40 (m, 1H), 1.37-1.22 (m, 2H).

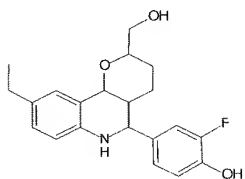
336



$^1\text{H}$  NMR (500 MHz, DMSO)  $\delta$  = 7.46-7.38 (m, 4H), 7.38-7.33 (m, 1H), 7.32 (s, 1H), 7.28 (dd,  $J$ =8.6, 1.9, 1H), 6.88 (s, 1H), 6.72 (d,  $J$ =8.5, 1H), 4.55 (d,  $J$ =11.5, 1H), 4.45 (d,  $J$ =2.2, 1H), 4.12 (dd,  $J$ =11.5, 6.5, 1H), 4.01 (dd,  $J$ =11.5, 3.7, 1H), 3.90-3.81 (m, 1H), 2.32 (t,  $J$ =7.3, 2H), 1.93-1.85 (m, 1H), 1.71-1.62 (m, 1H), 1.57-1.49 (m, 3H), 1.36-1.25 (m, 4H), 0.87 (t,  $J$ =7.4, 3H).

Chemistry 191

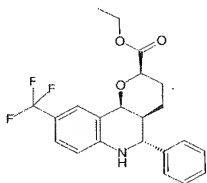
342



$^1\text{H}$  NMR (500 MHz, DMSO, mixture of isomers, 3:2 trans:cis)  $\delta$  = 9.70 (s, 1H), 7.15 (dd,  $J$ =12.4, 1.7, 0.6H), 7.04-6.99 (m, 1H), 6.99-6.90 (m, 1H), 6.90-6.79 (m, 2.4H), 6.57 (d,  $J$ =8.1, 0.4H), 6.50 (d,  $J$ =8.2, 0.6H), 6.14 (d,  $J$ =2.9, 0.4H), 5.78 (s, 0.6H), 4.54 (s, 1H), 4.39 (d,  $J$ =11.3, 0.6H, trans), 4.36 (d,  $J$ =5.2, 0.4H, cis), 4.29 (d,  $J$ =2.3, 0.6H), 4.16 (t,  $J$ =3.1, 0.4H), 3.61-3.51 (m, 0.6H), 3.46-3.40 (m, 1H), 3.40-3.34 (m, 1.4H), 2.44 (qt,  $J$ =11.0, 5.5, 2H), 2.08-2.02 (m, 0.4H), 1.83-1.68 (m, 1H), 1.65-1.53 (m, 1H), 1.49-1.36 (m, 1H), 1.36-1.22 (m, 2H), 1.16-1.05 (m, 3H).

Chemistry 184

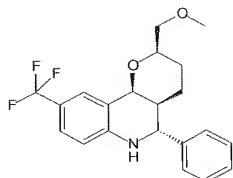
345



$^1\text{H}$  NMR (500 MHz, DMSO)  $\delta$  = 7.49-7.28 (m, 7H), 6.94 (s, 1H), 6.74 (d,  $J$ =8.6, 1H), 4.54 (dd,  $J$ =6.8, 4.6, 2H), 4.35-4.30 (m, 1H), 4.13 (q,  $J$ =7.1, 2H), 1.94 (d,  $J$ =11.6, 1H), 1.79-1.69 (m, 2H), 1.67-1.58 (m, 1H), 1.35-1.28 (m, 1H), 1.20 (t,  $J$ =7.1, 3H).

Chemistry 175

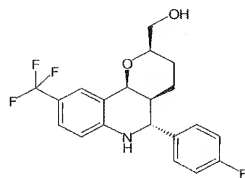
349



$^1\text{H}$  NMR (500 MHz, DMSO)  $\delta$  = 7.46-7.38 (m, 4H), 7.37-7.32 (m, 2H), 7.29 (d,  $J$ =8.6, 1H), 6.87 (s, 1H), 6.71 (d,  $J$ =8.5, 1H), 4.54 (d,  $J$ =11.5, 1H), 4.44 (d,  $J$ =2.1, 1H), 3.83-3.75 (m, 1H), 3.40 (dd,  $J$ =10.3, 6.0, 1H), 3.32 (dd,  $J$ =10.3, 6.0, 1H), 3.26 (s, 3H), 1.91-1.85 (m, 1H), 1.71-1.59 (m, 1H), 1.57-1.45 (m, 1H), 1.35-1.22 (m, 2H).

Chemistry 215

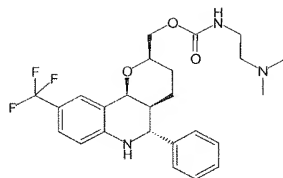
350



$^1\text{H}$  NMR (500 MHz, DMSO)  $\delta$  = 7.48 (dd,  $J$ =8.1, 5.8, 2H), 7.35 (s, 1H), 7.28 (d,  $J$ =8.5, 1H), 7.23 (t,  $J$ =8.7, 2H), 6.84 (s, 1H), 6.70 (d,  $J$ =8.5, 1H), 4.62-4.55 (m, 2H), 4.42 (d,  $J$ =1.4, 1H), 3.67-3.57 (m, 1H), 3.45 (quint,  $J$ =5.6, 1H), 3.40-3.33 (m, 1H), 1.87 (d,  $J$ =11.3, 1H), 1.69-1.59 (m, 1H), 1.54-1.44 (m, 1H), 1.37-1.24 (m, 2H).

Chemistry 214

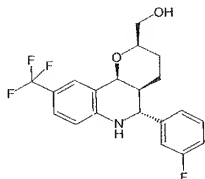
352



Chemistry 212

$^1\text{H}$  NMR (500 MHz, DMSO)  $\delta$  = 7.47-7.38 (m, 4H), 7.37-7.26 (m, 3H), 7.08 (t,  $J$ =5.2, 1H), 6.89 (s, 1H), 6.72 (d,  $J$ =8.5, 1H), 4.57 (d,  $J$ =11.5, 1H), 4.44 (s, 1H), 4.05-3.91 (m, 2H), 3.85-3.78 (m, 1H), 3.05 (dd,  $J$ =12.6, 6.2, 2H), 2.26 (t,  $J$ =6.7, 2H), 2.12 (s, 6H), 1.89 (d,  $J$ =11.0, 1H), 1.74-1.48 (m, 2H), 1.34-1.25 (m, 2H).

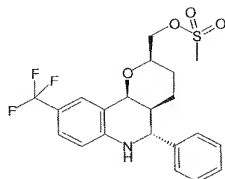
363



Chemistry 600

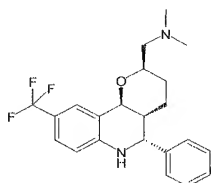
$^1\text{H}$  NMR (500 MHz, DMSO)  $\delta$  = 7.48-7.42 (m, 1H), 7.36 (d,  $J$ =1.6, 1H), 7.32-7.25 (m, 3H), 7.21-7.14 (m, 1H), 6.90 (s, 1H), 6.71 (d,  $J$ =8.5, 1H), 4.62-4.56 (m, 2H), 4.43 (d,  $J$ =2.3, 1H), 3.66-3.59 (m, 1H), 3.46 (quint,  $J$ =5.6, 1H), 3.4-3.34 (m, 1H), 1.93-1.87 (m, 1H), 1.66 (tt,  $J$ =13.7, 4.5, 1H), 1.56-1.45 (m, 1H), 1.38-1.25 (m, 2H).

564



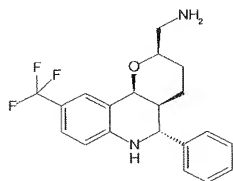
$^1\text{H}$  NMR (500 MHz, DMSO)  $\delta$  = 7.48-7.39 (m, 4H), 7.39-7.32 (m, 2H), 7.30 (dd,  $J$ =8.6, 1.9, 1H), 6.91 (s, 1H), 6.72 (d,  $J$ =8.6, 1H), 4.57 (d,  $J$ =11.5, 1H), 4.51 (d,  $J$ =2.1, 1H), 4.29-4.20 (m, 2H), 3.98-3.92 (m, 1H), 3.16 (s, 3H), 1.94-1.89 (m, 1H), 1.74-1.53 (m, 2H), 1.37-1.27 (m, 2H).

575



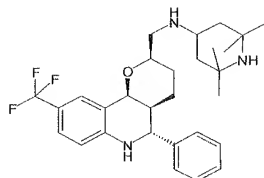
$^1\text{H}$  NMR (500 MHz, DMSO, HCl salt)  $\delta$  = 10.12 (s, 1H), 7.51 (d,  $J$ =1.5, 1H), 7.48-7.39 (m, 4H), 7.36 (t,  $J$ =7.0, 1H), 7.30 (dd,  $J$ =8.6, 1.9, 1H), 6.93 (s, 1H), 6.73 (d,  $J$ =8.6, 1H), 4.59 (d,  $J$ =2.2, 1H), 4.55 (d,  $J$ =11.5, 1H), 4.11 (s, 1H), 3.23-3.16 (m, 2H), 2.84-2.77 (m, 6H), 1.97-1.92 (m, 1H), 1.73-1.64 (m, 1H), 1.60-1.49 (m, 1H), 1.38-1.24 (m, 2H).

576



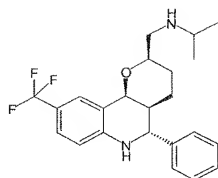
$^1\text{H}$  NMR (500 MHz, DMSO)  $\delta$  = 7.47-7.38 (m, 4H), 7.37-7.32 (m, 2H), 7.28 (dd,  $J$ =8.6, 1.9, 1H), 6.86 (s, 1H), 6.71 (d,  $J$ =8.5, 1H), 4.54 (d,  $J$ =11.4, 1H), 4.41 (d,  $J$ =2.2, 1H), 3.55-3.48 (m, 1H), 2.63 (dd,  $J$ =12.9, 6.2, 1H), 2.57 (dd,  $J$ =12.9, 4.9, 1H), 1.93-1.81 (m, 1H), 1.68-1.55 (m, 1H), 1.54-1.40 (m, 3H), 1.38-1.32 (m, 1H), 1.28 (d,  $J$ =13.7, 1H).

582



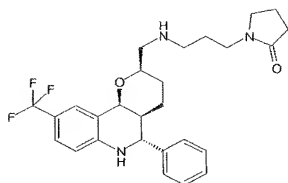
$^1\text{H}$  NMR (500 MHz, DMSO, HCl salt)  $\delta$  = 7.95 (s, 2H), 7.46-7.38 (m, 4H), 7.38-7.33 (m, 2H), 7.28 (dd,  $J$ =8.6, 1.6, 1H), 6.89 (s, 1H), 6.71 (d,  $J$ =8.6, 1H), 4.56 (d,  $J$ =11.4, 1H), 4.45 (d,  $J$ =1.7, 1H), 4.31 (d,  $J$ =4.2, 1H), 3.18 (s, 1H), 2.77 (s, 2H), 1.99-1.84 (m, 3H), 1.70-1.50 (m, 2H), 1.42 - 1.18 (m, 18H).

584



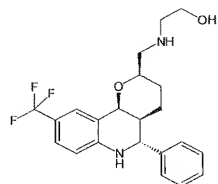
$^1\text{H}$  NMR (500 MHz, DMSO, HCL salt)  $\delta$  = 8.71 (s, 1H), 8.48 (s, 1H), 7.51-7.39 (m, 5H), 7.36 (t,  $J$ =7.1, 1H), 7.30 (dd,  $J$ =8.6, 1.9, 1H), 6.94 (s, 1H), 6.73 (d,  $J$ =8.6, 1H), 4.59 (d,  $J$ =11.5, 1H), 4.49 (d,  $J$ =2.2, 1H), 3.98 (t,  $J$ =10.0, 1H), 3.12-2.91 (m, 2H), 1.94 (d,  $J$ =11.5, 1H), 1.74-1.51 (m, 2H), 1.43-1.35 (m, 1H), 1.29 (d,  $J$ =13.1, 1H), 1.23 (t,  $J$ =7.0, 6H).

586



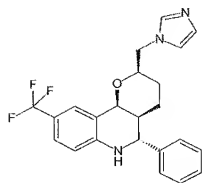
$^1\text{H}$  NMR (500 MHz, DMSO)  $\delta$  = 8.36 (s, 2H), 7.48-7.44 (m, 3H), 7.42 (t,  $J$ =7.4, 2H), 7.36 (t,  $J$ =7.1, 1H), 7.29 (dd,  $J$ =8.6, 1.8, 1H), 6.93 (s, 1H), 6.73 (d,  $J$ =8.6, 1H), 4.58 (d,  $J$ =11.5, 1H), 4.49 (d,  $J$ =2.0, 1H), 3.95 (t,  $J$ =9.3, 1H), 3.35-3.16 (m, 4H), 3.08-2.91 (m, 2H), 2.86-2.81 (m, 2H), 2.21 (t,  $J$ =8.1, 2H), 1.97-1.86 (m, 3H), 1.86-1.77 (m, 2H), 1.74-1.63 (m, 1H), 1.63-1.53 (m, 1H), 1.36 (d,  $J$ =12.1, 1H), 1.28 (d,  $J$ =12.4, 1H).

588



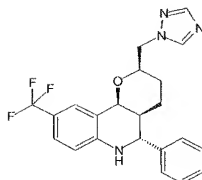
$^1\text{H}$  NMR (500 MHz, DMSO, HCl salt)  $\delta$  = 8.65 (d,  $J$ =32.7, 2H), 7.49-7.457 (m, 3H), 7.42 (t,  $J$ =7.4, 2H), 7.36 (t,  $J$ =7.2, 1H), 7.30 (dd,  $J$ =8.6, 1.9, 1H), 6.94 (s, 1H), 6.73 (d,  $J$ =8.6, 1H), 5.21 (t,  $J$ =5.0, 1H), 4.58 (d,  $J$ =11.5, 1H), 4.49 (d,  $J$ =2.2, 1H), 4.01 (t,  $J$ =9.9, 1H), 3.68 (dd,  $J$ =10.4, 5.2, 2H), 3.16-3.00 (m, 4H), 1.97-1.86 (m, 1H), 1.72-1.53 (m, 2H), 1.36 (d,  $J$ =11.2, 1H), 1.28 (d,  $J$ =12.6, 1H).

599



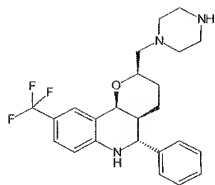
$^1\text{H}$  NMR (500 MHz, DMSO)  $\delta$  = 14.52 (s, 1H), 9.05 (s, 1H), 7.70 (d,  $J$ =1.0, 2H), 7.48-7.41 (m, 4H), 7.40-7.34 (m, 1H), 7.30 (d,  $J$ =8.2, 1H), 7.25 (s, 1H), 6.93 (s, 1H), 6.73 (d,  $J$ =8.5, 1H), 4.53-4.47 (m, 2H), 4.39 (dd,  $J$ =14.0, 3.1, 1H), 4.33-4.25 (m, 1H), 4.08-4.02 (m, 1H), 1.97-1.924 (m, 1H), 1.77-1.62 (m, 1H), 1.57-1.47 (m, 1H), 1.41 (d,  $J$ =12.8, 1H), 1.32 (d,  $J$ =13.6, 1H).

600



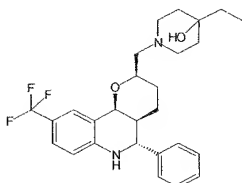
$^1\text{H}$  NMR (500 MHz, DMSO)  $\delta$  = 8.44 (s, 1H), 7.97 (s, 1H), 7.44-7.38 (m, 4H), 7.38-7.32 (m, 1H), 7.31-7.26 (m, 1H), 7.25 (s, 1H), 6.89 (s, 1H), 6.71 (d,  $J$ =8.5, 1H), 4.50 (d,  $J$ =11.5, 1H), 4.47 (d,  $J$ =2.2, 1H), 4.35-4.26 (m, 2H), 4.08-4.00 (m, 1H), 1.90 (d,  $J$ =11.4, 1H), 1.71-1.60 (m, 1H), 1.59-1.46 (m, 1H), 1.35-1.23 (m, 2H).

602



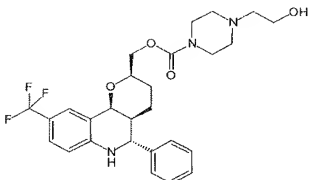
$^1\text{H}$  NMR (500 MHz, DMSO, HCL salt)  $\delta$  = 11.70 (s, 1H), 10.03-9.77 (m, 2H), 7.72 (d,  $J$ =1.6, 1H), 7.48-7.40 (m, 4H), 7.39-7.34 (m, 1H), 7.29 (dd,  $J$ =8.6, 1.9, 1H), 6.73 (d,  $J$ =8.6, 1H), 4.58 (d,  $J$ =2.2, 1H), 4.54 (d,  $J$ =11.5, 1H), 4.30-4.10 (m, 5H), 3.81 (s, 1H), 3.71 (s, 1H), 3.55-3.42 (m, 4H), 1.99-1.93 (m, 1H), 1.75-1.64 (m, 1H), 1.62-1.47 (m, 1H), 1.36 (d,  $J$ =12.9, 1H), 1.30 (d,  $J$ =13.6, 1H).

607



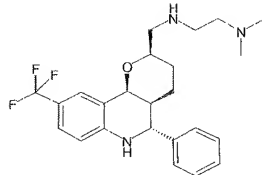
$^1\text{H}$  NMR (500 MHz, DMSO)  $\delta$  = 9.45 (s, 1H), 7.54-7.39 (m, 5H), 7.36 (t,  $J$ =6.8, 1H), 7.29 (d,  $J$ =7.1, 1H), 6.91 (s, 1H), 6.72 (d,  $J$ =8.6, 1H), 4.63-4.43 (m, 3H), 4.13 (s, 1H), 3.50-3.05 (m, 5H), 1.98-1.92 (m, 1H), 1.87-1.25 (m, 10H), 0.84 (t,  $J$ =7.2, 3H).

611



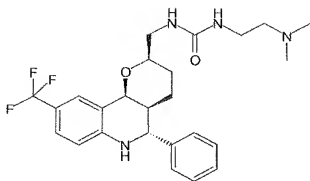
$^1\text{H}$  NMR (500 MHz, DMSO)  $\delta$  = 7.46-7.38 (m, 4H), 7.38-7.32 (m, 2H), 7.29 (d,  $J$ =8.6, 1H), 6.88 (s, 1H), 6.72 (d,  $J$ =8.5, 1H), 4.54 (d,  $J$ =11.5, 1H), 4.46 (d,  $J$ =2.1, 1H), 4.38 (t,  $J$ =5.4, 1H), 4.08 (dd,  $J$ =11.3, 6.3, 1H), 3.99 (dd,  $J$ =11.3, 3.9, 1H), 3.89-3.80 (m, 1H), 3.50 (q,  $J$ =6.0, 2H), 3.37 (s, 4H), 2.44 – 2.33 (m, 6H), 1.94-1.87 (m, 1H), 1.73-1.60 (m, 1H), 1.60-1.47 (m, 1H), 1.37-1.25 (m, 2H).

623



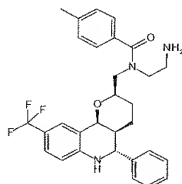
$^1\text{H}$  NMR (500 MHz, DMSO)  $\delta$  = 7.47-7.39 (m, 5H), 7.36 (t,  $J$ =7.0, 1H), 7.30 (dd,  $J$ =8.6, 1.8, 1H), 6.93 (s, 1H), 6.73 (d,  $J$ =8.6, 1H), 4.57 (d,  $J$ =11.5, 1H), 4.50 (d,  $J$ =2.1, 1H), 3.95 (t,  $J$ =10.0, 1H), 3.07-2.92 (m, 4H), 2.65-2.53 (m, 3H), 2.25 (s, 6H), 1.97-1.90 (m, 1H), 1.72-1.61 (m, 1H), 1.60-1.49 (m, 1H), 1.36 (d,  $J$ =12.8, 1H), 1.29 (d,  $J$ =13.1, 1H).

626



$^1\text{H}$  NMR (500 MHz, DMSO)  $\delta$  = 7.46-7.38 (m, 4H), 7.38-7.32 (m, 2H), 7.29 (dd,  $J$ =8.6, 1.9, 1H), 6.91 (s, 1H), 6.72 (d,  $J$ =8.6, 1H), 6.06 (t,  $J$ =5.7, 1H), 5.91 (t,  $J$ =5.5, 1H), 4.58 (d,  $J$ =11.5, 1H), 4.42 (d,  $J$ =2.2, 1H), 3.65-3.56 (m, 1H), 3.19-3.01 (m, 4H), 2.24 /t,  $J$ =6.4, 2H), 1.91-1.82 (m, 1H), 1.67-1.57 (m, 1H), 1.55-1.39 (m, 1H), 1.31-1.20 (m, 2H).

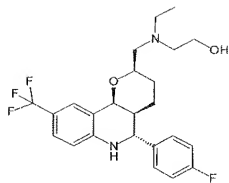
629



$^1\text{H}$  NMR (500 MHz, DMSO, d-TFA exchanged)  $\delta$  = 7.55-7.07 (m, 11H), 6.78 (d,  $J$ =8.5, 1H), 4.57-4.36 (m, 2H), 3.79 (s, 2H), 3.52-3.35 (m, 3H), 3.19-3.03 (m, 2H), 2.34 (s, 3H), 2.02-1.90 (m, 1H), 1.75-1.55 (m, 2H), 1.41-1.22 (m, 2H).

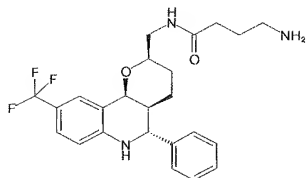


644



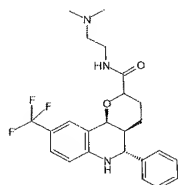
$^1\text{H}$  NMR (500 MHz, DMSO, HCL salt)  $\delta$  = 9.95 (s, 1H), 9.77 (s, 1H), 8.81 (s, 1H), 7.62- 7.44 (m, 3H), 7.35-7.20 (m, 3H), 6.89 (s, 1H), 6.73 (d,  $J=8.5$ , 1H), 5.44-5.20 (m, 1H), 4.57 (d,  $J=7.8$ , 1H), 4.18 (s, 1H), 3.76 (s, 2H), 3.30-3.15 (m, 4H), 2.95 (s, 1H), 1.94 (d,  $J=11.1$ , 1H), 1.75-1.65 (m, 1H), 1.62-1.50 (m, 1H), 1.37 (d,  $J=10.8$ , 1H), 1.31-1.17 (m, 4H).

645



$^1\text{H}$  NMR (500 MHz, DMSO, HCL salt)  $\delta$  = 8.02 (t,  $J=5.7$ , 1H), 7.78 (s, 3H), 7.47-7.39 (m, 4H), 7.39-7.32 (m, 2H), 7.29 (dd,  $J=8.6$ , 1.9, 1H), 6.89 (s, 1H), 6.72 (d,  $J=8.5$ , 1H), 4.56 (d,  $J=11.4$ , 1H), 4.43 (d,  $J=2.2$ , 1H), 3.71-3.61 (m, 1H), 3.21-3.17 (m, 2H), 2.82-2.75 (m, 2H), 2.23 (t,  $J=7.2$ , 2H), 1.92-1.87 (m, 1H), 1.82-1.71 (m, 2H), 1.67-1.58 (m, 1H), 1.51-1.40 (m, 1H), 1.36-1.21 (m, 2H).

652



$^1\text{H}$  NMR (500 MHz, DMSO)  $\delta$  = 7.50-7.24 (m, 6H), 6.96 (s, 1H), 6.75 (d,  $J=8.6$ , 1H), 5.76 (s, 1H), 4.61-4.54 (m, 2H), 4.08 (dd,  $J=11.2$ , 2.5, 1H), 3.25-3.08 (m, 2H), 2.40-2.33 (m, 1H), 2.33-2.24 (m, 2H), 2.21-2.05 (m, 6H), 1.99-1.88 (m, 1H), 1.82-1.51 (m, 2H), 1.39-1.21 (m, 2H), .

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

09.02.2010  
Date

Jan Hauß